DOCKET NO.: M0656.70098US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	John Landers et al.
Serial No.:	10/676,154
Confirmation No.:	7775
Filed:	September 29, 2003
For:	METHODS AND PRODUCTS RELATED TO GENOTYPING AND DNA ANALYSIS
Examiner:	Katherine D. Salmon
Art Unit:	1634

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

In response to the Final Office Action mailed November 6, 2009 (hereinafter, "OA 11/6/09," paper numbers not available on PAIR), Applicants hereby request Panel Review. The rejections of record are not proper, and are without basis, for the reasons discussed below. Claims 149, 150, 153-160, 165, and 166 have been rejected under 35 U.S.C. §103, while claims 151 and 152 have been objected to.

Overview

Applicant's invention relates to a high throughput method for genotyping. The methods disclosed and claimed in the instant application involve detecting the presence or absence of a single nucleotide polymorphism (SNP) allele in a genomic DNA sample by preparing a reduced complexity genome (RCG) from the genomic DNA sample. The method for making the RCG recited in the claims is a randomly primed polymerase chain reaction (PCR). A "randomly primed PCR-reduced complexity genome" is a reproducible representative fraction of the genomic DNA that is used for further analysis and is composed of multiple DNA fragments having random sequences and identical regions. (Specification, pp. 15-16.) A SNP is but one of many possible types of polymorphisms known to those of skill in the art; a SNP can be considered a species within the genus of polymorphisms. The methods also require that the RCG is analyzed by hybridization for the presence or absence of a SNP allele, for instance with a SNP-ASO. Further, claims 149, 150, 154-158, and 160 require that the polymorphic loci corresponding to the SNP-ASOs are present with a frequency of at least 50% in the RCG, and claim 166 requires that they are specific for the RCG. Claim 165 requires that the arrayed panel of ODN are indicative of SNP alleles associated with the RCG. These recitations require that the SNP alleles desired to be analyzed, and thus represented by the SNP-ASOs, are present within the RCG. Thus the RCG is designed such that it will include the genomic sequences that

correspond with the SNP-ASOs. Claim 166 meets this same goal by including the limitation that the analysis produces the genotype of the subject. Without having a correspondence between the RCG and the arrayed panel of SNP alleles, it would not be possible to accurately predict the genotype.

Applicant has established through arguments previously submitted that the citation of art combining a sub-genomic sample of reduced complexity with an ODN array does not provide a *prima facie* rejection of the claims. This combination relies on hindsight and elements of the claims are missing from the combination. The rejection of record includes both legal and factual deficiencies as discussed below.

Rejection under 35 U.S.C. §103(a)

Claims 149, 150, 154-158, 160, 165, and 166 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lisitsyn, *et al.*, *Science*, 259:946-951 (1993) ("Lisistyn") in view of Nikiforov, *et al.*, Int. Pat. Apl. Pub. No. WO 95/15970 ("Nikiforov") (OA 11/6/09, pp. 4-8). The rejection of claims 165 and 166 has been maintained over Cheung, *et al.*, *Proc. Natl. Acad. Sci. USA*, 93:14676-79 (1996) ("Cheung") in view of Nikiforov (OA 11/6/09, pp. 8-13). Dependent claims 153 and 159 have been rejected in view of Lisistyn and Nikiforov in view of Cheung.

Each rejection of record fails to establish a *prima facie* rejection of the claims, as each pending claims contains at least one non-obvious narrowing limitation not found in this combination of references. To establish a *prima facie* case of obviousness, the Office must provide a combination of references that includes all of the claimed elements. Since Lisistyn is newly cited, Applicant addresses the rejection below rather than referring to prior Office Actions. However, the arguments are similar in nature to prior arguments of record. Cheung has been addressed in prior Office Actions and responses.

Lisitsyn describes a new method for cloning the differences between two complex genomes, which may result in the identification of probes for a special type of polymorphism referred to therein as PARFs (pages 946 and 950). The method, referred to as RDA, involves the production of driver and tester amplicons (subset of the genome). The tester amplicon, with adapters added, is hybridized to driver amplicon and amplification of the double stranded tester is performed to achieve subtraction. The amplified products are cloned and analyzed to identify PARFs.

Claims 149, 150, 154-158, 160: The combination of references does not produce the inventions claimed in independent claim 149 and 157 because neither Lisistyn nor Nikiforov (summarized in a Response filed 5/26/09, p. 6) discloses or suggests polymorphic loci corresponding to the SNP-ASOs that are present with a frequency of at least 50% in the RCG. The OA 11/6/09 appears to be completely silent regarding this recitation, which is legally insufficient. Moreover, such a limitation would not be predictable to one of ordinary skill in the art when starting from a randomly-primed PCR-derived RCG (reduced complexity genome). There is no teaching in either Lisistyn or Nikiforov of starting with an RCG containing *less than 20%* of the genomic material present in a whole genome, then exposing the RCG to a plurality of oligonucleotides chosen such that the oligonucleotides collectively contain *at least 50%* of the polymorphic loci potentially found within the RCG, as is recited in claims 149 and 157.

Nowhere do either Lisistyn or Nikiforov explain how such a subset of oligonucleotides could be selected to have such properties. For example, as stated in the OA 11/6/09, Lisitsyn does not teach using RCG fragments to detect SNPs or genotype, nor exposing the RCG fragments to a surface comprising oligonucleotides, let alone selecting the oligonucleotides such that the nucleotides contain at least 50% of the polymorphic loci corresponding to the oligonucleotides present within the RCG.

Nikiforov likewise does not teach using polymorphic loci corresponding to oligonucleotides that are present with a frequency of at least 50% in the RCG. Nikiforov instead appears to be relied on only for the teaching that oligonucleotides attached to a surface can be exposed to products amplified using PCR techniques. For instance, in Example 11A, Nikiforov teaches that PCR amplification can be used to detect a known polymorphism in a horse genome. However, factually, this example does not teach or suggest using an RCG, instead merely teaching amplification of a *single*, specific region of the horse genome (chosen using two specific primer sequences 18 and 19) to determine a single polymorphism.

It is not predictable, based on the teaching of Nikiforov that a *specific* portion of the genome can be studied for the presence of a polymorphism, that one could *randomly* chose 20% of a whole genome to produce an RCG, and expose the RCG to a set of oligonucleotides such that the oligonucleotides can be used to determine at least 50% of the polymorphisms present within the RCG. Indeed, because of the randomization involved in creating the RCG, one of ordinary skill in the art would instead predict that, for such a method to work, the *entire* genome, not just a relatively limited portion of it, would be needed in order to capture at least 50% of the polymorphisms present within the RCG. Such an unexpected result (capturing and determining at least 50% of the polymorphisms present in any randomly-selected portion that is 20% or less of the entire genome) is not predictable from the teachings of Nikiforov.

Accordingly, since no combination of Lisistyn or Nikiforov, to the extent they can be combined (which is not conceded), discloses or suggests polymorphic loci corresponding to the SNP-ASOs that are present with a frequency of at least 50% in the RCG made using the at least one PCR primer, as is recited in independent claim 149 and 157, the combination of Lisistyn or Nikiforov is improper.

Claims 153 and 159: These claims depend from claims 149 and 157, respectively. As claims 149 and 157 have been discussed above, claims 153 and 159 are patentable for at least these reasons. It is also not conceded that there would have been any rational reason to combine Lisistyn, Nikiforov, and Cheung.

Claims 165 and 166: Regarding independent claims 165 and 166, the Office has not shown where Lisistyn or Nikiforov teach or suggest "hybridizing said RCG with an arrayed panel of oligonucleotides *indicative of SNP alleles* associated with said RCG," as is recited in claim 165, or "hybridizing said RCG with an arrayed panel of SNP alleles *specific for* said RCG," as is recited in claim 166. (Emphasis added). The OA 11/6/09 fails to discuss these recitations, which is legally insufficient.

As discussed above, and as stated in the OA 11/6/09, factually, Lisitsyn does not teach using RCG fragments to detect SNPs or genotype, nor exposing the RCG fragments to an arrayed panel of oligonucleotides. Likewise, Nikiforov does not teach such an arrayed panel of oligonucleotides or SNP

alleles associated with or specific for a RCG. Example 11A of Nikiforov is directed to amplification of a single, specific region of the horse genome to determine a single polymorphism, and thus does not teach using an arrayed panel that is able to detect more than one SNP allele. Nowhere does Nikiforov teach the use of an arrayed panel of oligonucleotides, let alone one that is indicative of SNP alleles in an RCG. In addition, it is not seen how an arrayed panel of oligonucleotides containing such SNP alleles that are specific for a reduced-complexity genome containing less than 30% of the genomic material from the entire genome could be predicted based on the teaching that a single polymorphism can be detected by amplifying a single, specific region of a horse genome.

Thus, since the combination of Lisistyn or Nikiforov, to the extent they can be combined (which is not conceded), fails to teach hybridizing an RCG with an arrayed panel of oligonucleotides indicative of SNP alleles associated with the RCG, or hybridizing an RCG with an arrayed panel of SNP alleles specific for the RCG, the combination of Lisistyn or Nikiforov is improper with respect to these claims.

Claims 165 and 166 have also been rejected over of Cheung in view of Nikiforov. The Office has not identified where either Cheung or Nikiforov teach or suggest "hybridizing said RCG with an arrayed panel of oligonucleotides indicative of SNP alleles associated with said RCG," as is recited in claim 165, or "hybridizing said RCG with an arrayed panel of SNP alleles specific for said RCG," as is recited in claim 166. This is legally insufficient. In fact, neither Cheung nor Nikiforov teaches or suggests using RCG fragments to determine the presence or absence of SNPs in an RCG, nor determining a genotype of a subject based on hybridization of RCG fragments to an arrayed panel of SNP alleles.

Applicant explained in the Response filed 5/26/09 why the combination of Cheung and Nikiforov did not produce the claimed invention. Specifically on pages 6-7, it is explained that without an array which is indicative of (claim 165) or specific for (claim 166) an RCG the skilled artisan would not have been able to determine the presence or absence of SNP alleles (165) or determine a genotype (166). Accordingly, since the combination of Cheung and Nikiforov, to the extent that these references can be combined (which is not conceded), fails to teach hybridizing an RCG with an arrayed panel of oligonucleotides indicative of SNP alleles associated with the RCG, or hybridizing an RCG with an arrayed panel of SNP alleles specific for the RCG, the combination of Cheung or Nikiforov is improper.

Additionally, it would not have been obvious for one of ordinary skill in the art to modify Lisitsyn's or Cheung's methods to look at SNPs (as required by the pending claims), because the skilled person would have had no motivation to do so. Further, the skilled person would not have combined them because there would be no expectation of success prior to the teachings of the instant invention. Each of the pending claims relates to detecting the presence or absence of a SNP allele. A SNP is defined in the instant application as "a single base pair (i.e., a pair of complementary nucleotide residues on opposite genomic strands) within a DNA region wherein the identities of the paired nucleotide residues vary from individual to individual." Many kinds of polymorphisms were known in the prior art. Examples of polymorphisms include deletions (depicted in Figure 4 of Lisitsyn), reciprocal translations

(depicted in Figure 4 of Lisitsyn), insertions and mutations, each of which may be one or more nucleotides in length. In contrast, a SNP is, by definition, a single nucleotide polymorphism.

First, Lisitsyn's and Cheung's methods involve genetic analysis generally and specifically PARFs (Lisitsyn) and microsatellite genotyping (Cheung). Lisitsyn and Cheung do not suggest that the method could be used to look at SNPs. Secondly, there is nothing in Lisitsyn or Cheung, even when combined with the prior art, that would have motivated the skilled person to examine only SNPs from among the vast genus of polymorphisms, or given that person a reasonable expectation of success in so doing.

A claim is not obvious if there is no suggestion in the art to make the claimed invention, or one of skill in the art would not have had a reasonable expectation of success in so doing. Noelle v. Lederman, 355 F.3d 1343, 1351-52, 69 U.S.P.Q.2d 1508, 1515 (Fed. Cir. 2004). The claims as construed are compared to what one of ordinary skill in the art would have considered obvious.

Cheung and Lisitsyn provide no motivation at all to look at SNPs as SNPs are not even mentioned therein. The methods described therein are in fact wholly inadequate to analyze SNPs without significant experimentation by the skilled person. The only methods taught for SNP analysis in the prior art were "specific PCR" based methods, in which specific segments of DNA molecules are amplified using primer sets specific for the particular segments. To analyze many SNPs at once, a skilled person would use many specific PCR reactions combined into a single amplification reaction (called "multiplex PCR"), using separate sets of primers for each specific PCR reaction. As described in Response filed 5/26/09, the skilled person would not have put a complex sub-genomic fraction on an array because it would be unclear if the allele being analyzed was present within the fraction. Thus, the skilled person would have had no reasonable expectation of success in using RCGs for SNP analysis.

Conclusion

Applicants respectfully request consideration of the above request and a favorable decision by the Panel. If there are any questions, the Panel is requested to call the undersigned at the telephone number listed below. If any fee is due, including an extension fee, please charge Deposit Account No. 23/2825.

Dated: May 6, 2010

Respectfully submitted,

By _____

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